Coombs test negative. There was a gross deficiency of erythrocyte G-6-PD. The patient was transferred to another job. After a month the blood findings had returned practically to normal; the urine contained no urobilin; and the serum bilirubin was 0.5 mg/100 ml.

We believe that the acute haemolytic crisis in this patient was due to nalidixic acid. The patient had not eaten broad beans nor taken any haemolysing drugs, nor had he come into contact with any other haemolysing substances in his work. We record this case to draw attention to the importance of G-6-PD-screening in subjects who are occupationally exposed to nalidixic acid or other haemolysing drugs.—We are, etc.,

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- 1 Belton, E. Margaret, and Vaughan Jones, R., *Lancet*, 1965, 2, 691.
- 2 Mandal, B. K., and Stevenson, J., *Lancet*, 1970, 1, 614.

E.B. Virus and Multiple Sclerosis

SIR,—The hypothesis that multiple sclerosis is a late manifestation of an infectious disease common in childhood was introduced by Poskanzer and colleagues.¹ Since then more than 30 virus antigens have been used to test antibodies in serum specimens from patients with multiple sclerosis and control subjects. Many studies have indicated that antibodies to measles virus are slightly but consistently raised in patients with multiple sclerosis compared with controls. The hypothesis implies that all viruses are suspected if they are able to cause persistent cell infection and can penetrate the central nervous system.

Epstein-Barr virus is known to cause relatively mild infections in children² and infectious mononucleosis in adolescents³ sometimes complicated by inflammation of the central nervous system.⁴ E.B. virus antibodies have not been studied earlier in this connexion. We therefore compared the titres of E.B. virus antibodies in serum specimens from 52 patients with multiple sclerosis, from 39 of their siblings, and from 52 carefully selected controls matched for age, sex, and place of residence to reveal the possible differences in antibody levels between the groups. Antibody titres to herpes simplex, varicella-zoster, and measles virus were also included in the results.

Antibodies to E.B. virus were tested by Henle's indirect immunofluorescence technique.⁵ Complement fixing antibodies to other herpesviruses and haemagglutinating antibodies to measles virus were tested as described.⁶ The results expressed as mean titres are shown in the Table.

Test	Geometric Mean		
	Multiple Sclerosis	Siblings	Controls
Measles H.I. . .	38.4*	28.8	26.7
Herpes C.F. . .	23.6	30.4	18.0
Zoster C.F. . .	4.2	4.4	4.2
E.B.V. F.A. . .	187.2	175.7	186.6

* The difference compared with the controls is statistically significant ($P < 0.05$)

The only statistically significant difference is seen in the measles H.I. test. The results do not indicate any connexion between the

herpesviruses, including E.B. virus, and multiple sclerosis.—We are, etc.,

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- 1 Poskanzer, D. C., Schapira, K., and Miller, H., *Lancet*, 1963, 2, 917.
- 2 Henle, G. and Henle, W., *Journal of Infectious Diseases*, 1970, 121, 303.
- 3 Henle, G., Henle, W., and Diehl, V., *Proceedings of the National Academy of Sciences, U.S.A.*, 1968, 59, 94.
- 4 Silverstein, A., Steinberg, G., and Nathanson, M., *Archives of Neurology*, 1972, 26, 353.
- 5 Henle, G., and Henle, W., *Journal of Bacteriology*, 1966, 91, 1248.
- 6 Panelius, M., et al., *Acta Neurologica Scandinavica* (in press).

Source of Contamination in Haemodialysis Equipment

SIR,—We wish to report a potential source of bacterial contamination in haemodialysis equipment using an external electrolyte standard. This was discovered while investigating a patient on intermittent haemodialysis who became pyrexial towards the end of each dialysis. Repeated blood cultures were sterile but *Pseudomonas aeruginosa* and *Alcaligenes* sp. were isolated from the dialysate entering the dialyser. The dialysate was supplied from a Lucas proportionating system which was disinfected between dialyses with formalin. Dialysate taken from the header tank contained both organisms but they were not isolated from the water or the concentrated dialysate supply. The organisms were also isolated from the external electrolyte standard which surrounds an electrode and is contained in a test-tube suspended in the header tank. When the test-tube is emptied or filled the electrode is frequently placed directly in the header tank, a procedure that would permit transfer of micro-organisms.

The electrolyte standard was prepared in the chemical pathology department using glucose-free concentrated dialysate and deionized water and was distributed in 500-ml glass-stoppered stock bottles. *Ps. aeruginosa* and *Alcaligenes* sp. were isolated from the electrolyte standard stock bottle of the patient under investigation and of another symptomless patient. All the strains of *Ps. aeruginosa* were indistinguishable by pyocine typing.

These findings suggest that the dialysate in the header tank became contaminated by the electrolyte standard solution. The standard is now distributed in 1-oz (28-ml) universal bottles and autoclaved before use.—We are, etc.,

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Interaction of Benzodiazepines with Tricyclic Antidepressants

SIR,—We were interested that Dr. M. Orme and others (9 September, p. 611) found that benzodiazepine drugs had no significant effect on plasma levels of warfarin. Their findings are pertinent to a study we have just completed to investigate possible interactions between various tranquillizing and hypnotic

drugs and the steady-state plasma levels of tricyclic antidepressants. Twelve psychiatric patients were studied and in none could we detect a significant alteration in the plasma level of nortriptyline attributable to benzodiazepine drugs. The drugs given were nitrazepam, chlordiazepoxide, diazepam, and oxazepam.

We did, however, demonstrate a lowering of plasma nortriptyline level in a smaller number of patients who were given amylobarbitone. This is in accord with earlier work showing that barbiturates induce hydroxylating enzymes causing increased metabolism of tricyclic drugs and resultant lowering of the steady state level.^{1,2}

We obtained puzzling results in a small number of patients who were given benzocetamine. The studies were too few to be more than only suggestive at this stage of a possible complex interaction. We feel that our results reinforce the conclusion of Dr. Orme and his colleagues that benzodiazepine drugs in man are remarkably free from interaction effects. We feel therefore that when anxiolytics are necessary in addition to tricyclic antidepressants they should be of this group and that nitrazepam should be the hypnotic of choice, particularly in depressed patients.—We are, etc.,

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- 1 Hammer, W., Idström, C. M., and Sjöqvist, F., in *Antidepressant Drugs*, ed. S. Garattini and M. N. G. Dukes, p. 301. Amsterdam, Excerpta Medica, 1967.
- 2 Alexanderson, B., Evans, D. A. Price, and Sjöqvist, F., *British Medical Journal*, 1969, 4, 764.

Nutritional Rickets in Immigrants

SIR,—Dr. J. A. Ford and others (19 August, p. 446) have drawn our attention to a situation which has concerned us for some time. We disagree with their conclusions that the high phytate content of unleavened bread is the major cause of late rickets and osteomalacia in Pakistani and Indian communities in Glasgow. They did not mention any of the well-established criteria for the diagnosis of osteomalacia such as clinical features, discovery of vitamin D and calcium deficiency in the diet, radiological and histological findings, and the exclusion of renal disease or malabsorption by appropriate tests. The serum calcium was not corrected to its protein concentration and there was no mention of serum alkaline phosphatase in healthy children of comparable age. Part of the rise in the serum alkaline phosphatase in their children could have been due to the pubertal spurt of growth.¹

Clearly calcium and phosphorus balance investigations would be necessary to determine the response to a chupatty-free diet and to implicate phytates in the aetiology of osteomalacia. Failing those, estimation of urinary calcium and total hydroxyproline excretion and data on the growth of these children during seven weeks' treatment would have provided some useful indication of healing bone disease. The authors do not mention low intake of calcium through the soft drinking water in Glasgow, which could be of significance in immigrant children with

borderline dietary intakes of calcium and vitamin D, particularly during the pubertal spurt of growth. It could contribute to the severity of vitamin-D lack osteomalacia in women.

We² have much experience of treating patients with nutritional osteomalacia in Lucknow, India, and we have not found any difference in the incidence of osteomalacia in communities eating largely rice, or maize, or wheat, or mixed cereals. We have always found a dietary deficiency of calcium and vitamin D, and nutritional osteomalacia is very rare in men and in women without children who are all taking the same amount of chupatty in the diet. We have found nutritional osteomalacia rare in Meerut, where the water is hard compared with Lucknow. There are, of course, also differences in diet. People in Lucknow lack foods containing vitamin D and calcium. Therefore the possibility that hardness of water may affect the prevalence of osteomalacia requires further investigation.

The observations of Dr. Ford and others implicating dietary phytates as an additional factor in the aetiology of osteomalacia are unconvincing. During the second world war the British national loaf, which had a high phytate content, was enriched with calcium. Most workers since have doubted whether this precaution was necessary. Walker and others³ found that normal people adapted after a few weeks to a high intake of phytate and absorbed enough calcium to maintain balance. Nicolaysen and Njaa⁴ also found that an intake of 800 mg (eight times more than in Dr. Ford's cases) of phytic acid daily in bread had a negligible effect when measured over a 12-week period and could recover in the faeces only 15% of the phytate which the diet provided. Vaishnav and Rizvi⁵ did not mention epidemiological investigations in nutritional rickets and, in fact, reported that dietary phytates play hardly any role in the causation of osteomalacia.

The skin synthesis of cholecalciferol and probably genetically-determined differences in the conversion of inactive vitamin D₃ to its active metabolites of 25-HCC and 1, 25-DHCC are some of the problems which warrant further studies in osteomalacia in immigrants. Calcium deficiency alone (phytates in Dr. Ford's series) does not produce rickets unless there is also a deficiency of vitamin D, and this, we believe, is the view of Dent and his group⁶ and others.⁷ This being so, the prophylactic treatment should be vitamin D and not extra calcium. Furthermore, vitamin D can be given as one large dose a year in the winter without any other dietary adjustment.—We are, etc.,

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Department of Human Metabolism,
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¹ Round, J. M., *British Medical Journal*, 1972, 3, 114.

² Teotia, S. P. S., and Teotia, M., *Lancet*, 1972, 1, 543.

³ Walker, A. R. P., Fox, F. W., and Irving, J. T., *Biochemical Journal*, 1948, 42, 452.

⁴ Nicolaysen, R., and Njaa, L. R., *Acta Physiologica Scandinavica*, 1951, 22, 246.

⁵ Vaishnav, H., and Rizvi, S. N. A., *Lancet*, 1972, 1, 750.

⁶ Dent, C. E., and Smith, R., *Quarterly Journal of Medicine*, 1969, 38, 195.

⁷ Fourman, P., and Royer, P., *Calcium Metabolism and the Bone*, 2nd ed., p. 288. Oxford, Blackwell Scientific, 1968.

Malaria in the U.K.

SIR,—Your epidemiology article on malaria in the U.K. (9 September, p. 652) is of value in underlining the problem but is spoilt by some surprising errors. It is true that in Africa there are no known strains of *Plasmodium falciparum* resistant to chloroquine but strains resistant to proguanil and pyrimethamine have been recognized for many years. The reports have been summarized by Peters.¹

A death rate of 35% in *P. falciparum* infections in West Africa, mainly in children under 5 years, is ridiculous. As in these areas of holoendemic malaria all children are infected before the age of 5 your figure suggests a child mortality of at least 300 per 1,000 from malaria alone. Though there is no doubt that malaria is an important, regrettable, and preventable cause of death in these children it is generally agreed that the correct figure is between 5% and 10% even in areas where most cases are untreated.² Perhaps your figure of a death rate of 35% is meant to refer to untreated malaria in non-immune expatriates visiting these areas.

It would have been better if your article had stressed the high mortality of *P. falciparum* malaria in this country—seven deaths in 138 cases. I suspect that most of these deaths could have been diagnosed, treated, and prevented if malaria had been considered a possible cause of sickness in patients who had recently visited Africa.—I am, etc.,

M. J. COLBOURNE

Ross Institute of Tropical Hygiene,
London W.C.1

¹ Peters, W., *Chemotherapy and Drug Resistance in Malaria*, London, Academic Press, 1970.

² Pampana, E., *A Textbook of Malaria Eradication*, 2nd edn. London, Oxford University Press, 1969.

** We referred this letter to our correspondents from the Public Health Laboratory Service, who after consulting the Malaria Reference Laboratory at Horton reply as follows: We do not agree that the figure of 35% for the death rate in *P. falciparum* infections in West Africa is "ridiculous"—for example, Sagent *et al.*¹ reported a death rate of 47% from the Congo among children under three years of age. In some parts of Africa there is less done to control and prevent and to treat malaria today than for many years, owing to the political situation in the Congo and the parts of Nigeria involved in the recent Biafran war.

The figure of 35% was certainly meant to refer to untreated malaria in non-immune persons. Dr. Colbourne is misleading in writing about drugs used for prophylaxis (proguanil and pyrimethamine) and treatment (chloroquine) as if they were one and the same thing: when discussing resistance we were referring to treatment and not prophylaxis. In treating cases in semi-immunes the mortality is about nil and in the past the Malaria Reference Laboratory has repeatedly stressed not only the importance of early diagnosis and treatment in primary *P. falciparum* cases among travellers recently returned from Africa, but also the preventable nature of the high mortality of *P. falciparum* infection in this country. Incidentally the figure of seven deaths in 138 cases is almost certainly an underestimate as there may be other cases—we are aware of at least one—not diagnosed or suspected during life—Ed., *B.M.J.*

¹ Sagnet, H., Morineaud, J. P., Revil, H., Thomas, J., and Masart, Y., *Médecine Tropicale*, 1967, 27, 606.

Dietary Fibre

SIR,—Before the Britons start running for bran in search of relief from constipation (Mr. C. Latto, 16 September, p. 705), or diverticular disease (Mr. N. S. Painter and others, 15 April, p. 137), or the maladies of civilization in general (Surgeon Captain T. L. Cleave, 13 May, p. 408), I hope they will pause and ponder. Will the phytic acid in bran upset the calcium metabolism? Will osteomalacia flourish again?

In 1935 a Fellow of the Royal College of Physicians of Edinburgh wrote¹ "Ispaghula is used with excellent results for . . . chronic constipation, with autointoxication from other causes . . . Ispaghula acts mechanically . . . is superior to liquid paraffin, is much cheaper and is further free from the injurious effects produced by the habitual use of the latter drug . . . chopra." I would plead for re-evaluation of ispaghula.—I am, etc.,

J. K. ANAND

Ilford, Essex

¹ Singh, J., *Modern Medical Treatment*, p. 11. Lahore, Civil and Military Gazette Press, 1935.

Allergy to House-dust Mites in the Tropics

SIR,—Drs. D. J. Buchanan and I. G. Jones, working in Zambia, found positive skin prick tests to *D. farinae* significantly more common in bronchial asthmatics than in controls (23 September, p. 764). Dr. J. Comney and I, working in Accra, Ghana, have made similar observations on 40 asthmatics and 60 controls. These findings are being published in detail elsewhere. We agree that allergy to house-dust mites may be important in the aetiology of asthma in the tropics. Asthma is a considerable problem in Accra and little is known about allergic factors. Groundnuts, rice, okro, yam, and cocoyam appear to be common precipitants of asthmatic attacks in Accra.—I am, etc.,

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Pantothenic Acid and Coeliac Disease

SIR,—In the clinicopathological conference report on a case of non-responsive coeliac disease (9 September, p. 624) no mention is made of administration of pantothenic acid. I should like to suggest that such patients with coeliac disease who respond only partially to a gluten-free diet may benefit from the administration of pantothenic acid.

It is known that pantothenic acid deficiency can produce atrophy of the small intestinal mucosa in all animal species,¹ and in many species ulceration of the gastric and intestinal mucosa can occur.² At necropsy the patient discussed had ulceration of the small and large intestine and villous atrophy despite having a gluten-free diet. Pantothenic acid deficiency can also produce impairment of adrenal function.³ It has previously been noted that "pseudo-hypoadrenalism" is commonly described in coeliac disease.⁴ This patient was noted to be pigmented. As she was on corticosteroids adrenal function tests were not mentioned.

Deranged carbohydrate metabolism occurs in pantothenate deficiency with decreased